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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,607	11/26/1997	JACQUES FASTREZ	370068-9650	4607

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EXAMINER	
SAIDHA, TEKCHAND	
ART UNIT	PAPER NUMBER
1652	23

DATE MAILED: 08/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
09/978607	Fastrez et al.	
Examiner T. Sandha	Group Art Unit 1652	23

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

X Responsive to communication(s) filed on (RCE) 4/8/02.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

X Claim(s) 13-29 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

X Claim(s) 13-29 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ ☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892 ☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948 ☐ Other _____

Office Action Summary

DETAILED ACTION

1. The amendment filed on 4.8.02 (Paper Nos. 16 & 17) and a Request for Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 08/978607 is acceptable and a RCE has been established. An action on the RCE follows.

2. Following RCE and the amendment cited above, a non-final Office Action is as follows.

3. Claims 13-29 are pending.

4. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments filed as per the above cited amendment have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

35 U.S.C. § 112, first paragraph

6. Claims 13-29 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a method of determining the amount of an analyte in a test sample using a chimeric β-lactamase as the starting enzyme, and comprising selected amino acids sequence insert in the loop of the rim of the active site residues 103-105, for example; or the alpha. 11 helix residues 271-272 of the R-Tem β-lactamase, for example; in order that the enzyme be defined as a chimeric enzyme, which are then selected for binding by antibodies psa10 and psa66. The claims are directed to a method of determining the presence of an analyte using any (a) chimeric enzyme as the starting enzyme, wherein said chimeric enzyme is constructed by inserting a sequence of said mimetope (binding site moiety) into a sequence of said starting enzyme by replacing at least one amino acid of

the starting enzyme with a sequence of said mimetope. However, the guidance provided for a single site specific chimeric β-lactamase is inadequate for one skilled in the art to develop a method using any chimeric enzyme construct for determining the presence or amount of an analyte in a test sample.

Factors to be considered in determining whether undue experimentation is required, are summarized in *re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) [*Ex parte* Forman [230 USPQ 546 (Bd. Pat. App. & Int. 1986)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim. The factors most relevant to this rejection are the scope of the claims, unpredictability in the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

The claims are directed to a method for determining the presence of an analyte in a test sample using any enzyme as the starting enzyme, modifying the enzyme(s) to create a functional or enzymatically active chimeric enzyme having a binding site moiety, to which a binding molecule can attach. From the guidelines provided for construction of chimeric β-lactamase and the skill of the artisan in the area of molecular biological and enzymology it would have been possible to modify the mimetope as evidenced by SEQ ID Nos. 1-78 which is inserted by replacing at least a single amino acid in the chimeric β-lactamase structure from any source in order to selectively modulate the catalytic activity of the β-lactamase upon binding. Selective insertion sites have been identified, for example, the loop preceding the alpha -11 helix (residues 271-272 of β-lactamase. However, the

transfer of such a construct to any enzyme from any source in order to first produce a chimeric enzyme and further attempt to selectively insert mimetopes pertinent to any enzyme in order to create a chimeric enzyme which can successfully attach itself to a binding molecules, lacks adequate guidance, is unpredictable and would result in undue experimentation. It lacks adequate guidance because the chimeric insertion developed for β-lactamase by insertion of the specific mimetopes to achieve binding in β-lactamase may not necessarily function with any enzyme and such a binding function for determining the presence or amount of an analyte in a test sample is neither exemplified nor is a matter of routine experimentation. This is because the modification of mimetope amino acid(s) and its insertion into any enzyme, including those not characterized yet will not necessarily result in producing an active chimeric enzyme in every other enzyme because every other enzyme is distinct in its sequence, regions of active site or susceptibility to modifications, leading to highly unpredictable results. Thus, the specification fails to provide guidance to other enzymes, other than β-lactamase and at the specific positions, that can be successfully utilized in effectively creating chimeric enzymes and the appropriate steps required for such constructs. Every enzyme being distinct , it remains unpredictable that the instant disclosure on β-lactamase be sufficient to develop a method for determining analytes using other any chimeric enzyme or any sequence insert (Clam 13) , which can successfully attach itself to any binding molecules (claims 14-19), or where the analyte and substrate contact the enzyme simultaneously or in steps (claims 20-25), or where the test sample contains the analyte (claim 25) or where the mimetopes is any one of the sequences of SEQ ID NOS : 1-78 (claims 26-27) or where the enzyme activity of the chemeric enzyme is in the unbound state

(claims 28-29). Therefore, the skilled artisan would require guidance, such as the (a) the sequence of the β-lactamase (SEQ ID NO:) or the other chimeric enzymes (by SEQ ID Nos:) and guidance to where the sequence inserts of the mimetope (BSM), identification of the active catalytic and binding sites and the effect(s) of such modifications on the functionality of the different enzymes constructs, in order to make and use chimeric enzymes in a manner commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

7. Applicants Arguments:

It must be emphasized that the above rejection is under 35 U.S.C. § 112, first paragraph (enablement) and is not a written description rejection.

Applicants have failed to address the key issues of the rejection. On page 19, for example, the Applicants incorporate a portion of a paragraph from the previous Office Action, which is out of context. It is unclear what evidence the Applicants are looking for from the examiner. Please point to the lines of the Office Action the Applicants are referring to, as it not clear what the basis of Applicants' following conclusion is :

"However, the Examiner appears to be assuming his own conclusion: he has presumed that there is substantial variation in the sequence among various species of β-lactamase.....The Examiner has not provided any evidence to support this conclusion".

Sequence homology or conservation of sequence homology is relied upon in order to evaluate how certain amino acid changes would effect or alter the enzyme activity. In the instant case, for example, if an amino acid change is made in the structure of a specific β-lactamase at a specific

position to obtain a chimeric β-lactamase, the same change and effect may be difficult to reproduce in another species of β-lactamase with a different structure, and even more difficult to obtain in another enzyme or protein or starting molecules, such as a transferase, an oxido-reductase, subtilisin, alkaline phosphatase, etc., having an entirely different structure or sequence. While it is known that many amino acid substitutions or replacement are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, catalysis and in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions. However, applicants have provided little or no guidance beyond the mere presentation of specific sequence inserts in β-lactamase to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in any enzyme (or protein) which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Such a definition might also read on previously characterized proteins, or alternatively, might include proteins with additional functions or activities neither envisioned nor enabled by applicants in the current invention. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988) with regard to the issue raised above.

Applicants further argue that the Examiner maintains, without any evidence to support his conclusion, that β-lactamase includes a diverse number of enzymes, presumably having dissimilar sequence homologies and functionalities.

In response, Applicants submission of the MINI-REVIEW (Bush et al. Antimicrobial Agents and Chemotherapy, 1995, 1211-1233), describes and supports the Examiner's point of view that there are diverse classes (A-D) of β-lactamases including Cephalosporins, Penicillin & β-lactams with differing sequence similarities. Figure 1, shows a dendrogram, describing the various β-lactamase and their structural relationships. Vertical branch lengths extending to the left are inversely proportional to the similarity between sequences.

Therefore a modification made in one type of the β-lactamase having a specific sequence may not necessarily translate to or appropriate to make in another kind of β-lactamase or any other enzyme.

8. Claims 13-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13-29 are directed to a method of determining the amount of analyte using any chimeric enzyme or 'the claimed genus' from any organism wherein any of the amino acid residues along the peptide chain is modified to make chimeric enzyme. Claim 24 recite a 'single species' in enzyme beta-lactamase. The specification describes amino acids inserts in the loop of the rim of the active site residues 103-105, for example; or the alpha. 11 helix residues 271-272 of the R-Tem β-

lactamase, for example; in order that the enzyme be defined as a chimeric enzyme, which are then selected for binding by antibodies psa10 and psa66. The prior art teaches the R-Tem beta-lactamase amino acid sequence which forms the reference or the base structure of the chimeric β-lactamase. The specification does not describe a representative number of species to the genus. A 'representative number of species' requires that the species which are expressly described be representative of the entire genus. Thus, when there is substantial variation within the genus, it may require a description of the various species which reflect the variation within the genus. In the instant case, however, the description of a single species of the chimeric β-lactamase is not representative of the entire genus which includes any of the other enzyme(s), as the various species reflect variation within the genus. Therefore, if a specific amino acid site is altered in the chimeric β-lactamase, without a clear description of the identities of equivalent site of β-lactamase from other species, such a alteration or modification may not result in having a similar effect in any genus or species claimed. What constitutes a 'representative number' is an inverse function of the predictability of the art. The number must be sufficient to identify the other members of genus. In an unpredictable art, such as the instant one, wherein a chimeric enzyme is made by insertion of specific mimetopes (SEQ ID NO : 1-78), adequate written description requirement of a genus cannot be achieved by disclosing only one species within the genus. In such a case, where the members of the genus being claimed are expected to vary widely in their identifying characteristics, such as structure or enzyme activity, due to the introduced changes in the mimetope sequence to alter a particular enzyme property, for example,

binding, written description for each member within the genus will be necessary. Therefore, the written description requirement is not satisfied.

9. No claim is allowed.

10. Applicants attention is drawn to the allowed product claims in 08/757425. The instant method claims of similar scope will be in a better condition for allowance.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

T. Saidha

Tekchand Saidha
Primary Examiner, Art Unit 1652
August 12, 2002